REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1-7, 18, and 21-22 are pending and currently under examination in the application. Notwithstanding the grounds for any rejection, claims 1 and 7 have been amended to more particularly point out and distinctly claim certain embodiments of the Applicants' invention. No new matter was added by the amendments. Support for the amendments can be found in the specification, for example, on page 6, lines 10-15; and page 60, lines 6-15.

Double Patenting

The Examiner advises that if claim 1 is found allowable, then claim 22 will be objected to under 35 U.S.C. § 101 for alleged statutory type double patenting. The Examiner asserts that claim 22, which relates to direct injection of the claimed cells, is a substantial duplicate of claim 1, since injection into the brain of a patient, as in claim 1, is necessarily direct injection.

Applicants traverse this rejection and submit that claim 1 is not a substantial duplicate of claim 22. For example, the specification describes that cells may be introduced into the brain of mammal by way of *direct* injection, by using a *shunt*, or by *other means* known to a person skilled in the art (*see, e.g.,* page 22, lines 8-12). Contrary to the Examiner's assertion, and as defined in the instant specification, injection into the brain may encompass more than just direct injection, *e.g.*, it may encompass using a shunt. Claim 1, therefore, is not coextensive in scope with claim 22.

Applicants submit that claims 1 and 22 satisfy the statutory double patenting requirements under 35 U.S.C. § 101, and respectfully request reconsideration and withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claims 1-7, 18, and 22 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that the instant claims omit essential steps relating to

predifferentiation of stromal cells into astrocytes. The Examiner also asserts that the recitation "immunologically isolated" is unclear.

Applicants traverse this rejection and submit that the instant claims are clear. Notwithstanding the basis for any rejection, claim 1 has been amended to recite the step of "pre-differentiating said isolated stromal cells into said astrocytes" prior to administration, rendering moot this rejection to the claims.

With regard to the recitation "immunologically isolated," Applicants note that the specification describes this recitation as referring to the encapsulation, containment or other *physical separation* of an implanted cell from *the body into which it is implanted* such that the cell is not exposed to and cannot be eliminated by the immune system of the body, and further describes that cells which are immunologically isolated are *administered* in a manner that *physically isolates* them from the recipient's immune system (*see, e.g.,* page 18, lines 12-23 of the specification). Applicants submit that a person of ordinary skill in the art can readily determine the metes and bounds of the claims from the above-noted description in the specification.

Applicants submit that claims 1-7, 18, and 22 satisfy the requirements of definiteness under 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

A. The Examiner rejects claims 1-7 and 17-18 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserts that the specification is non-enabling for administering stromal cells pre-differentiated into astrocytes for the treatment of a disease, disorder or condition of the central nervous system, since the specification allegedly fails to "reasonably predict" whether said administration would *effect* therapy in humans.

Applicants respectfully traverse the Examiner's grounds for rejection and submit that the specification is commensurate in scope with the claims. Consistent with the purpose of the enablement requirement, the specification teaches a person skilled in the arts how to *make* and *use* the presently claimed subject matter without undue experimentation.

The Law

In the context of the *Wands* factors, as outlined in the instant Action, enablement rejections under 35 U.S.C. § 112, first paragraph, which are based on an alleged lack of disclosure relating to therapeutic efficacy, as here, must be analyzed under the same legal standard as a rejection under 35 U.S.C. § 101. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Accordingly, enablement rejections under 35 U.S.C. § 112 are improper when based on alleged lack of evidence regarding human therapeutic implementation, as the Federal Circuit has emphatically rejected the position that human clinical testing is necessary. *See Id.*

In particular, if data generated using *in vitro* assays, or from testing in an animal model or a combination thereof, is "reasonably correlated" to the particular therapeutic utility, the data will almost invariably be sufficient to establish therapeutic utility. *See* M.P.E.P. § 2107.03, citing, *inter alia*, *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995). Applicants note that such rejections by the Examiner have been uniformly reversed where an Applicant supplied a *reasonable evidentiary showing* supporting an asserted therapeutic utility, and that only in those cases where the Applicant was unable to come forward with *any relevant evidence* to rebut a finding that the claimed subject matter was *inoperative* was such a rejection confirmed by the court. *See* M.P.E.P. § 2107.03, citing *In re Citron*, 325 F.2d 248, 253 (CCPA 1963) (therapeutic utility for an *uncharacterized* biological extract not supported or scientifically credible) (emphasis added). As detailed herein, Applicants have hardly failed to come forward with *any relevant evidence* to support the asserted utility of the presently claimed method. On the contrary, Applicants have come forward with more than a reasonable evidentiary showing by providing, as described in greater detail below, working examples of stromal cells/astrocytes stably engrafted into the rat brain, detailed guidance on making and using the presently claimed subject matter, and evidence of the understanding of a person skilled in the art at the time of filing, which evidence demonstrates a *reliance* on animal models, such as those described herein, in determining the utility of stromal cells in transplant therapy of the central nervous system.

Despite the Examiner's abundant use of the term "reasonable predictability" in the instant Action, Applicants submit that the Examiner is failing to apply the correct legal standard. In particular, the Examiner focuses improperly on the predictability of the ultimate therapeutic

outcome, such as *effecting* the actual treatment of a disease or condition, as opposed to focusing properly on whether a person skilled in the art would accept that the presently claimed method *may* provide a therapeutic *utility*, as determined by the "reasonable predictability" of the animal model disclosed in the specification.

As one way of illustrating the proper standard, Applicants note that the evidentiary standard for entering human clinical trials is *significantly higher* than the therapeutic utility standard under 35 U.S.C. § 101, and thus § 112, first paragraph. *See, e.g.,* M.P.E.P. § 2107.03 at 2100-36. Under the standard for entering clinical trials, for example, an Applicant must provide to those especially skilled in the art (*e.g.,* the Food and Drug Administration (FDA)) a credible rationale of how a treatment *might* be effective, or *could* be effective. *Id.* As such, even under the presumably higher standard for clinical trials, an Applicant to the FDA is not required to demonstrate that a treatment will actually *effect* therapy with a degree of predictably as expected by the Examiner (*see* the Action, page 11), but instead must only show that a treatment *might* or *could* effect therapy. Accordingly, Applicants' evidence from an art-accepted animal model and accompanying rationale, as detailed herein, which shows that stromal cell/astrocyte transplantation *might* or *could* effect therapy, should be more than adequate to satisfy the presumably lower standard under the utility prong of the enablement requirement.

Moreover, Applicants note that the Examiner should not rely on post-filing date references to demonstrate that a claimed invention is not enabled, unless a person skilled in the art states that the invention is not possible years after the filing date. *See* M.P.E.P § 2164.05(a), citing *In re Wright*, 999 F.2d 1557, 1562, (Fed. Cir. 1993). Despite the Examiner's citation of boilerplate statements about the need for further research, the central teachings of the cited post-filing references actually support Applicants' position that it is possible to practice the presently claimed subject matter. The Examiner's reliance on such post-filing references as a basis for rejecting the instant claims is thus problematic.

Breadth of the Claims

The instant claims relate, in pertinent part, to *providing* astrocytes to a patient suffering from a disease, disorder or condition of the central nervous system, wherein the

astrocytes are derived from the bone marrow stromal cells of a syngeneic donor, and administering the astrocytes by injection into the patient's brain in single or multiple administrations of about 10^5 to about 10^{13} cells per 100 kg patient.

Regarding the breadth of the claims, Applicants respectfully disagree with the Examiner's assertion that the specification must be enabling for each disclosed use, such as for therapy of any condition of the central nervous system (*see* the Action, page 6). Applicants note instead that if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. *See* M.P.E.P. § 2164.01(c).

Nature of the Invention and the State of the Prior Art

With regard to the state of the prior art, Applicants respectfully disagree with the Examiner's assertions to the contrary and submit that the instant specification describes an animal model that is "reasonably correlated" to the asserted therapeutic utility, according to the understanding of a person skilled in the art at the time of filing. Applicants further submit that the Examiner's reliance on the cited art references is problematic in multiple respects. For one, as detailed below, certain of the cited references are neither technically relevant to the particular subject matter recited in the instant claims (*e.g.,* Bartley *et al.*; Swallow *et al.*; Horn *et al.*), nor are they relevant to the enablement requirement (*e.g.,* Bartley *et al.*; Keller *et al.*). The Examiner also selectively cites certain references to indicate the potential problems in highly *specific* areas of somatic cell therapy (*e.g.,* Bartley *et al.*), while ignoring both the successes of others and the evidence of their reliance on animal models similar to the models described herein (*e.g.,* Zawada *et al.*; Savitz *et al.*). In addition, the Examiner improperly relies on post-filing references, since, as noted herein, the Examiner should not rely on post-filing date references unless a person skilled in the art states that a particular invention is not possible years after the filing date. *See* M.P.E.P § 2164.05(a), citing *In re Wright*, 999 F.2d 1557, 1562, (Fed. Cir. 1993). As detailed below, none of the authors in the post-filing references, such as Bartley *et al.*, Savitz *et al.*, and Horn *et al.*, state that the presently claimed method is not possible, but, as is normal with scientists, merely weigh the recognized benefits in view of the potential problems with somatic cell therapy in general.

The Examiner relies on Bartley *et al.* (*Expert Opin. Biol. Ther.*, 3:541-49 (2003)) to outline some of the problems encountered in relying on somatic cell therapy to *effect treatment* in cerebral palsy, which, despite being specific to stem cell treatments in a particularly rare form of cerebral palsy, apparently suffices to delineate some of the problems with other such therapies in (*see* the Action, page 8). As previously made of record, however, Applicants submit that the concerns raised in Bartley *et al.* are not technically relevant to determining the utility of the presently claimed subject matter, as these concerns are too limited to relate to the use of stromal cell transplants as presently claimed. In essence, Applicants submit that the Examiner is attempting to have it both ways, by relying on the few, cerebral palsy-related critical statements in Bartley *et al.* to support the *broad* assertion that all forms of stromal cell therapy are not reasonably predictive of therapy in humans, while entirely ignoring the fact that Bartley *et al.* recognize many successful, reasonably predictive animal models for stromal cell therapy similar to the presently claimed method, merely because these animal models are described in *post-filing* references (*see, e.g.,* Mezey *et al.*, *PNAS USA* 100:1364-1369 (2003); Li *et al.*, J. *Cerebral Blood Flow Metal.* 20:1311-1319 (2000); Akiyama *et al.*, *J. Neuroscience* 22:6623-6630 (2002); Hess *et al.*, *Stroke* 33:1362-1368 (2002); and Zhao *et al.*, *Exp. Neurol.* 174:11-20 (2002), all of which are detailed in Applicants' Response of October 15, 2007). When viewed in the entirety, however, Bartley *et al.* provide sufficient evidence to show that a person skilled in the art would reasonably rely on small animal models in deciding whether a particular stromal cell related therapeutic approach *might* be effective, or *could* be effective, which evidence is more than adequate under the utility prong of the enablement requirement.

The Examiner relies on Swallow *et al.* (*Restorative Neurology and Neuroscience* 15:297-303 (1999)) to support the assertion that structure (cells) may not be sufficient for therapy, unless the required functional connections form as well. But Applicants note that physical, functional connections are not necessarily required for therapeutic utility. For example, Bradbury *et al.* (*Neuroscience* 65:955-72 (1995)) emphasize the usefulness of astrocytes in the repair of nervous system injury, showing that astrocyte transplants following chemically induced lesions to the nucleus basalis and medial septal regions lead to improved memory function. In fact, Bradbury *et al.* conclude that regeneration of cognitive function following grafting is most likely

mediated via *diffuse* graft-host communication, with *trophic secretion* a probable factor. In other words, and contrary to the Examiner's line of reasoning, Bradbury *et al.* identify a therapeutic utility for astrocyte grafts that does not require the functional connections described in Swallow *et al.*, but instead may rely on soluble factors. Functional utility relating to secretion factors is also relevant to certain embodiments as presently claimed, wherein the cells are "immunologically isolated." According to Bradbury *et al.*, and contrary to the Examiner's assertion (*see* the Action, page 14), isolated stromal cells, including immunologically isolated stromal cells, *could* affect certain types of therapy without forming functional connections and/or without physically integrating into the central nervous system. Overall, the Examiner's reliance on Swallow *et al.* as a basis for rejecting the instant claims is thus inappropriate.

The Examiner's reliance on Keller *et al.* (*Neuroscience* 98:149-56 (2000) is also problematic. In particular, the Examiner cites Keller *et al.* as one example of a disease state in which cellular *replacement* would not be sufficient, since the underlying pathology (degradation of spinal cord by proteosomes) would still exist following transplant. This assertion may be so, but, as noted herein, Applicants need not provide enablement for every possible central nervous system condition, because if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. *See* M.P.E.P. § 2164.01(c). As such, the Examiner's reliance on Keller *et al.* for a single, exemplary central nervous system condition that may or may not be treatable by cellular replacement *alone* is not necessarily relevant in view of the actual enablement requirement.

The Examiner relies on Horn *et al.* (*Molec. Ther.* 10:417-431 (2004) for the broad assertion that *small* animal models are not reasonably predictive of treatment in humans. As previously made of record, however, Applicants submit that this reference has little or no bearing on the presently claimed subject matter. Horn *et al.* merely show that transduction of hematopoietic cells in *large* animal models is more predictive of human hematopoietic transduction efficiency that transduction in *small* animal models. But Horn *et al.* is not pertinent to the presently claimed methods, as the conclusions in Horn *et al.* are specific to *gene transfer* therapies (*see, e.g.,* page 417, column 1, Introduction). The instant claims relate instead to *tissue* transplant therapies, such as donor cell engraftment in the central nervous system. Zawada *et al.*

provide a more pertinent outlook on the presently claimed methods, suggesting that the results from transplantation of tissues in the rat brain is a *good predictor* of the behavior and survival of these tissues in the human brain (*see, e.g.,* page 68, lines 17-20 of the specification), and demonstrating that somatic cell transplants improve disease symptoms in *human* patients with Parkinson's disease (*Nat. Med.* 4:569-574 (1998)). Zawada *et al.* thus provide evidence of a person skilled in the art relying on the behavior of somatic cell transplants in rodent models to predict the utility of potential transplant sources in treating Parkinson's disease. As such, the Examiner's reliance on Horn *et al.* is problematic for its lack of technical relevance to the subject matter of the instant claims, especially in view of the more pertinent evidence in Zawada *et al.*

The Examiner relies on Savitz *et al.* (*Cardiovasc. Nurs.* 18:57-61 (2003) in asserting that stromal cells are not reasonably predictive for treating stroke recovery, and relies in particular on the statement in Savitz *et al.* that answering therapeutically related questions "will require **extensive investigation**." But mere mention of the need for further research is not equivalent to a statement that a particular invention is not possible. In reality, basic science authors *always* ring a note of caution, and almost invariably mention that most therapies will require *extensive investigation*. These boilerplate, peripheral statements, however, are not relevant to the central teachings in the cited references, including Savitz *et al.* Zawada *et al.*, and Bartley *et al.*, which validate that it is possible to practice the claims as recited. For example, as previously made of record, Savitz *et al.* confirm the *predictive* value of stromal cell transplant rodent models in acknowledging that preclinical *animal data* has set the stage for early phase clinical trials using stromal cell to treat stroke victims. In fact, as a general rule, if an Applicant for patent has initiated human clinical trials for a therapeutic process, Office personnel should *presume* that the Applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility. *See* M.P.E.P. § 2107.03 at 2100-36. By analogy to this general PTO rule, in moving directly from rodent models to human clinical trials, Savitz *et al.,* therefore, provide a clear example of a person skilled in the art accepting that stromal cell transplant related rodent models are reasonably predictive of therapeutic utility in humans.

In further contrast to the Examiner's selectively negative view of the state of the art, Gage (*Nature* 30;392(6679 Suppl):18-24 (1998)) argues that cell therapy has emerged as a

strategy for the treatment of many human diseases. In particular, Gage suggests that the *source* and the *desired function* of the cell will dictate which cell type is most useful for each disease, citing concerns related to *immunological compatibility*, ability to multiply cells *in vitro* before transplantation, and general issues of quality control. Applicants note that as a *source* of cells, the presently claimed stromal cells are syngeneic, do not exhibit signs of an immune response in the transplant recipient (*see, e.g.,* page 68, lines 20-23), are easily cultured and multiply readily *in vitro* (*see, e.g.,* page 43, line 11 to page 44, line 2), pre-differentiate readily into astrocytic containing cell populations (*see, e.g.,* page 60, lines 6-15), and stably implant into the brain, expressing astrocytic markers and exhibiting the morphology of epithelioid flat astrocytes (*see, e.g.,* page 68, lines 6-17 of the specification).

Moreover, a person skilled in the art recognizes that astrocytes represent a therapeutically useful cell in transplant therapy, demonstrating many *desired functions*. For example, astrocytes have been shown to promote axonal regeneration and myelination in injured, adult rat brains (Wunderlich *et al.*, *Glia* 10:49-58 (1994)), to alter the microenvironment to prevent scar tissue formation following spinal cord injury, thus allowing improved regrowth of nerve fibres (Wang *et al.*, *Neuroscience* 65:973-81 (1995)), induce regeneration of severed dorsal root axons (Kikucih *et al.*, *Neurol Med Chir (Tokyo)* 33:682-90 (1993), and improve memory function following chemically induced lesions to the nucleus basalis and medial septal regions of the central nervous system (Bradbury *et al.*, *Neuroscience* 65:955-72 (1995)). Numerous *pre-filing* references thus recognize the therapeutic utility of transplanting astrocytes into the central nervous system, as recited in the instant claims.

Based on the evidence of the state of the art as provided herein, Applicants submit that a person skilled in the art would accept the isolated stromal cell/astrocyte related animals models described in the instant specification as being reasonably predictive of utility in humans, and that evidence from these tests should be considered sufficient to support the credibility of this utility.

The Direction and Guidance Provided By Applicant

The specification teaches a person skilled in the art by example how to *make* the claimed stromal cells using routine experimentation. For example, the specification provides exemplary guidance on isolating, enriching, expanding, and pre-differentiating stromal cells into astrocytes, as recited in the claims (*see, e.g.,* 54, lines 3-21; and page 60, lines 6-16). A person skilled in the art can determine whether donor stromal cells are syngeneic, as recited in the instant claims, according to routine techniques well-known in the art. Applicants note, as is also relevant below, that a "patent need not teach, and preferably omits, what is well-known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524, 1534 (Fed. Cir. 1987).

The specification also teaches a person skilled by example how to *use* the stromal cells as claimed using routine experimentation. For instance, as disclosed in the specification and recited in the claims, a person skilled in the art may administer the presently claimed cells by direct injection into the brain, using single or multiple administrations of between about 10^5 and about 10^{13} cells per 100 kg. The specification provides exemplary guidance in determining the fate of stromal cells predifferentiated into astrocytes administered to a mammal, and in particular demonstrates how to determine whether the cells properly differentiate and/or associate with the desired tissue (*see, e.g.,* page 65, line 1 to page 66, line 4 of the specification). A person skilled in the art may also assess biological markers for improvement in a mammal, such as axonal regeneration and myelination, using routine techniques known in the art, including those outlined in Wunderlich *et al.* (*Glia* 10:49-58 (1994), in addition to less invasive techniques, such as functional magnetic resonance imaging of the human brain, as described in Turner *et al.* (*Exp Brain Res*. 123:5-12 (1998)). Additional biological markers may include measurements of dopamine synthesis as assayed by flurodopa uptake by positron emission tomography (*see, e.g.,* page 63, lines 13-17 of the specification). Following direct injection, a person skilled in the art can, therefore, use the guidance provided in the specification and the knowledge in the art to routinely determine the fate of the transplanted cells, and to routinely determine any biological affects on the central nervous system therefrom.

A person skilled in the art can also routinely diagnose and identify any mammal having any disease, disorder or condition of the central nervous system, such as a genetic disease,

a tumor, trauma or stroke, as recited in certain embodiments of the instant claims. Once the mammal and disease are both identified, a person skilled in the art can routinely treat the disease by administering stromal cells predifferentiated into astrocytes to the mammal as discussed herein. Routine clinical parameters exist in the art for monitoring these treatments, including, for example, measurements of memory and/or neurocognitive function by electroencephalography, as exemplified by Gevins (*Electroencephalogr Clin Neurophysiol.* 106:165-72 (1998)), and/or more basic measurements of neuro-physical impairment, as exemplified by Roth *et al.* (*Arch Phys Med Rehabil.* 79:329-35 (1998). Applicants note that "a *considerable* amount of experimentation is permissible, if it is merely routine," particularly when "great expenditures of time and effort are ordinary" in a given field (*See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (quoting the Board of Patent Appeals and Interferences, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this [vaccine] art.")). As detailed herein, each of the steps necessary to *make* and *use* the presently claimed subject matter, as either provided in the specification or well-known in the art, are routine to a person skilled in the art and, thus, can be performed without undue experimentation.

The Existence of Working Examples

An *in vivo* animal model example in the specification constitutes a "working example" if that example "reasonably correlates" with a disclosed or claimed method, as understood by a person skilled in the art. *See* M.P.E.P. § 2164.02 at 2100-196. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka,* 753 F.2d 1040, 1050 (Fed. Cir. 1985) ("[A] rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence). Here, the specification demonstrates isolation and expansion of stromal cells, and predifferentiation of such cells into astrocytes (*see, e.g.,* page 60, lines 6-15). As noted by the Examiner (*see* the Action, page 17), the instant specification also demonstrates *in vivo* migration and stable integration of transplanted stromal cells/astrocytes into the rat brain, and in particular into the contralateral cortex and the temporal lobe regions, which cells express glial fibrillary acidic protein (GFAP), a marker for astrocyte differentiation (*see, e.g.,*

page 62, lines 8-12; and page 67, line 1 to page 69, line 9). Moreover, the recipient mammals showed no signs of either an immune reaction against the transplanted cells or any behavioral deterioration, supporting the safety of such cells in transplant therapy (*see, e.g.,* page 68, lines 20-23).

Given both the reliance on stromal cell transplant rodent animal models for predicting therapeutic utility in humans (*see, e.g.,* Zawada *et al.*; and Savitz *et al.*, as detailed above), and the acknowledged therapeutic properties of astrocytes in such transplants (*see, e.g.,* Wunderlich *et al.*; Wang *et al.*; Kikucih *et al.*; and Bradbury *et al.*, as detailed above), Applicants submit that a person skilled in the art at the time of filing would conclude that the examples provided in the specification "reasonably correlate" with a method of *providing* isolated stromal cells predifferentiated into astrocytes to a human patient suffering from a disease, disorder or condition of the central nervous system. As such, the instant specification provides working examples of the presently claimed subject matter, which examples provide evidence of enablement under the *Wands* factors.

Quantity of Experimentation

Applicants submit that given the breadth of the claims as discussed herein, the detailed guidance provided in the specification, the presence of working examples, the high level of skill and knowledge in the art, the evidence on the state of the art, which demonstrates a consistent reliance on somatic cell transplant rodent models to provide predictions on the potential for human therapeutic utility, and the proper evidentiary standard for determining therapeutic utility under the enablement requirement, Applicants have provided a *reasonable evidentiary showing* in support of the asserted utility, such that a person skilled in the art can practice the presently claimed subject matter using routine experimentation, and thus, without undue experimentation.

Accordingly, Applicants submit that claims 1-7, 18, and 21-22 are commensurate in scope with both the specification and the understanding of a person skilled in the art, satisfying the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully request withdrawal of this rejection to the claims.

B. The Examiner further rejects claims 1-7, 18, and 21-22 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, asserting that method steps critical to the practice of the claimed subject matter, but not included in the claims, is thus not enabled by the disclosure. In particular, as in the above-noted indefiniteness rejection under 35 U.S.C. § 112, second paragraph, the Examiner asserts that the claims fail to recite a step of predifferentiating stromal cells into astrocytes.

Applicants traverse this rejection and submit that the instant claims satisfy the enablement requirement. Nonetheless, merely to expedite prosecution, claim 1 has been amended to recite the step of "pre-differentiating said isolated stromal cells into said astrocytes," obviating the Examiner's grounds for this rejection.

Applicants submit that claims 1-7, 18, and 21-22 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection to the claims.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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